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Michael L. Goldman, Esq.
NIXON PEABODY LLP
Clinton Square
P.O. Box 31051
Rochester, NY 14603

EXAMINER

MONTANARI, DAVID A

ART UNIT PAPER NUMBER

1632

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/849,082

Applicant(s)

SUN, PIERA S.

Examiner

David Montanari

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 May 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date ____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: ____.

DETAILED ACTION

1. Claims 1-17 are examined in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 1 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 1 encompasses any transgenic organism, the scope of which encompasses a human being, which is non-statutory subject matter. As such, the recitation of the limitation "non-human" would be remedial. See 1077 O.G. 24, April 21, 1987.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of nucleic acid delivery into a fertilized shrimp egg comprising providing a fertilized egg prior to its formation of a protective layer; providing a nucleic acid molecule; and combining the nucleic acid molecule and the fertilized egg under conditions effective to allow the nucleic acid molecule to be delivered into the egg, does not reasonably provide enablement for a method of nucleic acid delivery into any fertilized egg. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-17 are drawn to a method of nucleic acid delivery into a fertilized egg comprising providing a fertilized egg prior to its formation of a protective layer; providing a nucleic acid molecule, and combining the nucleic acid molecule and the fertilized egg under conditions to allow the nucleic acid molecule to be delivered into the egg.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses the generation of a transgenic fertilized egg from any species of animal.

Whereas the nature of the invention is a method of delivery of a nucleic acid molecule to a fertilized egg before the formation of a protective layer, the art teaches that the claimed method

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is unpredictable. The art teaches that with regard to egg fertilization, certain requirements are necessary before fertilization can occur. One of these requirements is the formation of a protective layer. In mammals, this protective layer is called the zona pellucida (ZP), which comprises three glycoproteins mZP1, mZP2, and mZP3 (Liu et al., 1996, PNAS, Vol. 93, pg 5431 col. 1 parags. 1-2). Disruption of the gene encoding mZP3, or removal of the zona pellucida, results in sperm not binding to the egg and subsequent infertility (Liu, pg. 5431, Abstract). In invertebrates, the protective layer is known as the jelly coat which comprises three distinct layers designated J1, J2, and J3 (Mozingo et al., 1999, Developmental Biology, Vol. 210, pg. 428 col. 1 parag. 1). The art continues that “if the jelly layer is removed, sperm are unable to fertilize the egg, suggesting that is essential for fertilization (Mozingo, pg. 428, col. 1 parag. 1 lines 6-8). The art continues that extracellular matrices surrounding eggs of vertebrates vary between phylogenetic groups, however they all contain members of the ZP glycoprotein family in their egg coats, which is the ZP in mammals, the vitelline envelope in amphibians, and the chorion in teleost fish (Mengerink et al., 2001, Glycobiology, Vol. 11, pg. 38R col. 2 parag. 2 lines 1-5). The art continues that in zebrafish the chorion comprises three morphologically distinct layers and contains four major proteins, including homologues to ZP2, and ZP3 (Mengerink, pg. 39R, col. 2 parag. 4 lines 2-8). In the medaka fish two groups of glycoproteins exist in the chorion, ZI-1,2 and ZI-3, whose precursors, choriogenin H and choriogenin L correspond to ZP2 and ZP3 (Mengerink, pg. 40R, col. 1 parag. 1). The art continues that is thought that the sperm bind to ZI-1,2 and ZI-3 to maneuver across the surface of the egg to lead to fertilization (Mengerink, pg. 40R, col. 1 parag. 1). Thus while the claimed method requires that the egg be fertilized before the formation of a protective layer, and this occurs in shrimp, the

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art teaches that eggs from species other than shrimp must contain a protective layer before fertilization can begin.

The working examples provided in the instant application teach that mature fertilized shrimp eggs contain large cortical specializations (rods) in their cortex. These rods reside in membrane crypts and are isolated from the external environment by a thin investment coat which surrounds the egg. When the eggs contact seawater in the form of spawning, their cortical rods are expelled and form an investment coat, which subsequently dissipates. At this stage, the egg is naked without any coating material. About 12-18 minutes after spawning, a new jelly layer begins to form around the egg's exterior, and that in approximately 20-45 minutes after spawning, the jelly layer is fully formed into a hatching membrane (pg. 19 lines 15-29). The specification continues that mature gravid female shrimp (*Litopenaeus vannamei*) were obtained from a local shrimp farm and immediately after spawning, the shrimp eggs were collected, concentrated, and transferred to 3 ml sterilized sea water in a petri dish and subjected to microinjection, electroporation, and transfection with jetPEI.TM (pg. 20 lines 3-8). The specification continues that an expression vector p β actP2-TSV-CP(AS) was used in the microinjection, electroporation, and transfection experiments (pg. 20 lines 10-32). In each of said experiments, positive detection of the expression vector was determined by RT-PCR and genomic PCR assay (pg. 24, Table 1, and pg. 28, Table 2).

Thus while the specification has disclosed successful nucleic acid delivery into fertilized shrimp eggs prior to the formation of a protective layer, the art teaches that eggs from other species of animals including fish require the formation of a protective layer prior to fertilization. Thus the skilled artisan would require and undo amount of experimentation without a predictable

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degree of success to practice the claimed invention, and thus the limiting the scope of the invention to a method of nucleic acid delivery into a fertilized shrimp egg comprising providing a fertilized egg prior to its formation of a protective layer; providing a nucleic acid molecule; and combining the nucleic acid molecule and the fertilized egg under conditions effective to allow the nucleic acid molecule to be delivered into the egg is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4, 6-7, 9, and 11-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Tseng et al. (2000, Theriogenology, Vol. 54, pgs. 1421-1432).

Claims 1-2, 4, 6-8, 9, and 11-13 are drawn to a method of nucleic acid molecule delivery into a fertilized egg comprising: providing a fertilized egg prior to its formation of a protective layer; providing a nucleic acid molecule; and combining the nucleic acid molecule and the fertilized egg under conditions effective to allow the nucleic acid molecule to be delivered into the egg, wherein the nucleic acid molecule is heterologous to the egg, wherein the nucleic acid molecule is in an expression vector, wherein the expression vector is a circular vector, wherein the expression vector and nucleic acid molecule comprises a label, wherein the eggs is from a species selected from a group of marine fish, freshwater fish, and crustaceans, and wherein the egg is a shrimp egg.

Tseng et al. teach the electroporation of tiger shrimp fertilized eggs with a pFLAG-CMV-1-BAP expression vector, which contains a DNA fragment of the bacterial alkaline phosphatase gene (pg. 1421, Abstract, lines 1-2). Tseng continues to teach that wild tiger shrimp zygotes were collected 30 minutes after spawning, and that the zygotes were washed 2-4 times with buffer to remove the jelly coat, which would have prevented the DNA from entering the zygote during electroporation (pg. 1422 parag. 3). Tseng continues to teach that the FLAG monoclonal antibody was used to detect expression in ovaries by evidence of a blue-purple color (pg. 1428, Fig. 5). Thus Tseng et al. clearly anticipates the invention of claims 1-2, 4, 6-7, 9, and 11-13.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 5, 10, and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tseng et al. (2000, Theriogenology, Vol. 54, pgs. 1421-1432), in view of Godbey et al. (1999, J. of Controlled Release, Vol. 60, pgs. 149-160).

Claims 3, 5, 10, and 14-17 are drawn to a method of nucleic acid molecule delivery into a fertilized egg comprising using a nucleic acid molecule that is homologous to said egg, wherein said expression vector is a linear vector, wherein said nucleic acid is a label selected from a the group consisting of a radio-active label, a fluorescent label, a chemiluminescent label, and a biotinylated label, the use of a transfection reagent with the nucleic acid molecule and the fertilized egg, wherein said transfection reagent is selected from the group consisting of a

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cationic lipid reagent, a liposomal cationic lipid reagent, a cationic non-liposomal lipid reagent, an activated dendrimer reagent, and a cationic polyethyleneimine reagent, wherein the transfection reagent is a cationic polyethyleneimine, and wherein the transfection reagent is a linear cationic polyethyleneimine reagent.

Tseng et al. teach the electroporation of tiger shrimp fertilized eggs with a pFLAG-CMV-1-BAP expression vector, which contains a DNA fragment of the bacterial alkaline phosphatase gene (pg. 1421, Abstract, lines 1-2). Tseng continues to teach that wild tiger shrimp zygotes were collected 30 minutes after spawning, and that the zygotes were washed 2-4 times with buffer to remove the jelly coat, which would have prevented the DNA from entering the zygote during electroporation (pg. 1422 parag. 3). Tseng continues to teach that the FLAG monoclonal antibody was used to detect expression in ovaries by evidence of a blue-purple color (pg. 1428, Fig. 5). Tseng does not teach using homologous nucleic acid delivery, using linear vectors, and transfection reagents, including cationic transfection reagents.

Godbey et al. teach that polyethyleimine (PEI) is a cationic polymer that is used successfully for the transfection of nucleic acid both *in vitro* and *in vivo* (pg. 149, Abstract, and pg. 157 col. 2 parag. 2). Godbey continues that PEI comes in two forms linear and branched, with the branched form of PEI yielding significantly greater success in terms of cell transfection (pg. 150 cols. 1-2). Godbey continues that PEI/DNA complexes can be used to deliver labels to a target tissue (pg. 156, Fig. 4), the process of delivery involves endocytosis, and the role of lipids both on the PEI complex as well as the cell membrane is important (pg. 156 col. 2 bridge pg. 157 col. 1 parag. 1). Godbey further teaches that phospholipids-coated PEI/DNA complexes might be

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released into cell nuclei by fusion with endosomal membranes of the target cell (pg. 157, col. 1 parag. 1). Godbey does not teach a method of nucleic acid molecule delivery into fertilized eggs.

Thus it would have been obvious to the artisan of ordinary skill at the time of filing to modify the method taught by Tseng in view of the teachings of Godbey to use a transfection reagent comprising a cationic polymer to introduce any nucleic acid molecule into a fertilized egg prior to its formation of a protective layer in view of the teachings and motivations of Tseng that shrimp fertilized eggs electroporated with an expression vector 30 minutes after spawning incorporate the expression vector into their genomic DNA and can further visualize the expression vector by immunohistochemistry, and in further view of the teachings and motivations of Godbey that cationic polymers can seemingly deliver any nucleic acid molecule to a target cell. Thus, the cited prior art provides the requisite teachings, suggestions, and motivation to make and use the claimed method.

Motivation is provided by Tseng et al. teaching the electroporation of shrimp fertilized eggs with an expression vector without the presence of a protective layer results in a significant uptake of said expression vector. Further motivation is provided by Godbey et al. teaching the advantages of using cationic polymers complexed with nucleic acid for delivery to target cells.


No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 1-571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Montanari, Ph.D


RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER